UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,820	10/12/1999	DANIEL G. CHAIN	20555/1203301-US1	6495

7278 7590 10/03/2006

DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,820	CHAIN, DANIEL G.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,23,24,33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,23,24,33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-14-06 has been entered.

The amendment filed 7-14-06 has been entered into the record. Claims 1-13, 15-22, 25-32, 34 and 36-37 have been cancelled. Claims 14, 23, 24, 33 and 35 are pending.

Rejections Withdrawn

Any rejection not specifically maintained herein is withdrawn in favor of the new grounds of rejection set forth below.

Rejections Maintained

Claim 14 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) for reasons made of record in the Office Actions mailed 4-22-03, 1-26-06 and herein.

The claim is drawn to a monoclonal antibody that is free-end specific for the free n-terminus of an amyloid beta peptide bind to said free N-terminus or said free N-terminus and does not bind to the amyloid beta-precursor protein from which said amyloid beta peptide may be proteolytically derived. The claims are not seen to require that the free N-terminus is AB(1-40) or soluble.

Saido et al teach a polyclonal antibody 9204, that was produced using a synthetic heaxamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet

hemocyanin. The antibody distinguished the fragments possessing the exact amino terminus of AB from the intact precursors and other fragments including the secretase products. Antibody 9204 also recognized synthetic AB1-40 peptide but not AB2-40 peptide. Furthermore, Saido et al teaches that binding of antibody 9204 to AFF-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or by AEFRHC. Said o et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that the usse of the cleavage site specific antibody provides for better relative quantitativeness. (see page 15254-55, column 1, Resultes, first and second paragraphs). Saido et al teaches that "similar approaches for producing the proteolygie product specific antigodies will be applicable to resolving the differential carboxyl-terminal processing of AB peptides...". Saido et al differs by not teaching a monoclonal antibody with the properties of polyclonal antibody 9204.

Takeda teaches that monoclonal antibodies that are specific for the N-terminal and C-terminal of AB are useful for the detection of AB1-40 and AB1-42 for the detection of AB species i*n vitro* (see page 5) Takeda teaches that AB1-40 is water soluble (page 4, lines 33-41). Takeda teach the N and C-terminal peptide sequence of AB1-40.

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of Saido et al to generate free-end N-terminal specific antibodies that do not bind the prescursor using the conventional techniques of Goding et al because of the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies. One would have been motivated to make monoclonal antibodies to decrease the lot to lot variability that can happen with polyclonal antisera and Takeda et al teach that the monoclonal antibodies are useful for the detection of AB1-40 and AB1-42 for the detection of AB

species *in vitro* and that AB1-40 is water soluble. One of ordinary skill in the art would have a reasonable expectation of success given the demonstrated immunogenicity of the epitope.

Applicants alledge that the claims have been amended that the antibody bind soluble amyloid peptide. This is not persuasive because the claims are not so limited. The construction of the claim is in the alternative, any free N-terminus or any amyloid beta peptide. Further, even if the claim did indicate free N-terminus of a soluble beta amyloid it is noted that the art as combined teaches that AB1-40 is soluble in water and therefore the antibody that is specifically binds the free N-terminal of AB1-40 would meet the alleged limitation. Further, the term soluble does not obviate the binding to the same region on water aggregating (insoluble) AB1-42 or AB1-43, because they all have the same free-end terminal. Since all the synthetic peptides are soluble in SDS the antibody would bind SDS soluble amyloid peptides. Applicants argue that the combination does not teach soluble beta amyloid. This is simply not so see the citation of Takeda set forth above. The art acknowledges that AB1-40 is water soluble. Therefore, the combination of record does not fail. The rejection is maintained.

Claims 23, 24 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee IDS Nov 16, 2001), Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claim 14 above and further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994) for reasons made of record in the Office Actions mailed 4-22-03, 1-26-06 and herein.

The claims are drawn to single chain antibodies that are free-N-terminal end specific for AB peptides and further limited to AB1-40, AB1-42 or AB1-42.

The teachings for Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as combined are set forth supra. The references as combined fail to teach single chain antibodies.

Seubert et al teaches the use of antibodies that bind AB peptides in *in vitro* or *in vivo* assays that screen for inhibitors of AB peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "... the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, VL, VH, and other fragments." Seubert et al also teach that "It would also be possible to employ recombinantly produced antibodies (immunoglobulins) and variation thereof as now well described in the patent and scientific literature. See, for example EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full pargraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of a single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the free-end, N-terminal specific monoclonal antibody according to the combination of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc.,

London 1983, pages 56-97) supra, by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produce that bind AB peptides are useful in a variety of detection techniques for use in screening or diagnostic assays.

New Rejections

Claims 14, 23, 24, 33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 as amended and claims 23, 24, 33 and 35 as dependent therefrom) makes no sense because it is unclear what "binds" actively modifies. The monoclonal antibody should specifically bind the free N-terminus or free C-terminus. The claim is further *prima facie* indefinite because "said free C-terminus of soluble amyloid peptide" lacks antecedent basis in the claims. The term "soluble" is not defined in the specification and the metes and bounds of this limitation cannot be readily ascertained because solubility of a peptide is determined by the particular solvent and the solvent is not set forth in the specification or the claims.

Claims 23 and 35 are *prima facie* indefinite because the claim cannot be a single chain antibody in accordance with a claim directed to a monoclonal antibody because a monoclonal antibody comprises 4 polypeptide chains. This issue may be resolved by redrafting this claim in independent format. Additionally, claim 35 is rejected for being confusing because each of the alternatives have the identical free N-terminal and as such do not properly represent alternative choices of N-terminal "free ends" because the all are identical.

Claim 14 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal fo Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97).

The claim is drawn to a monoclonal antibody that is free-end specific for the free C-terminus of amyloid beta peptide AB1-40 bind said free C-terminus of soluble amyloid peptide and does not bind to the amyloid beta-precursor protein from which said amyloid beta peptide may be proteolytically derived.

Takeda teaches that monoclonal antibodies that are specific for the N-terminal and C-terminal of AB petides are useful for the detection of AB1-40 and AB1-42 for the detection of AB species i*n vitro* (see pages 4-5). Takeda teaches that AB1-40 is water soluble (page 4, lines 33-41). Takeda teach the N and C-terminal peptide sequence of AB1-40. Takeda teach the monoclonal antibody BA-27a, that was considered to be specific for the C-terminus of beta amyloid (1-40), and weakly cross-reacted to beta-amyloid (1-38), (1-39) and beta amyoid (1-42) with a cross reactivity with 2% or less (page 34, lines 41-46). Takeda et al differs by not teaching a monoclonal antibody that has no cross-reactivity as "uniquely recognizes" the free C-terminal of AB1-40 and does not recognize the precursor.

Saido A teaches a polyclonal antibody 9204, that was produced using a synthetic heaxamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet hemocyanin for the N-terminal of AB1-40. The antibody distinguished the fragments possessing the exact amino terminus of AB from the intact precursors and other fragments including the secretase products. Antibody 9204 also recognized synthetic AB1-40 peptide but not AB2-40 peptide. Furthermore, Saido et al teaches that binding of antibody 9204 to AFF-C100 was inhibited by the haptenic peptide DAEFRC, but not by

MADEFTC or by AEFRHC. Said o et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that the use of the cleavage site specific antibody provides for better relative quantitativeness. (see page 15254-55, column 1, Resultes, first and second paragraphs). Saido et al teaches that "similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of AB peptides...". Saido et al teach that their unique methodology for producing such proteolytic produce-specific antibodies now seems to have general applicability (page 15254 (column 1, see first paragraph results section).

Saido B teaches an general technique for producing antibodies that specifically distinguish a proteolyzed form from a given intact form and are free-end specific.

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of the Saido A and B to generate free-end C-terminal specific AB1-40 monoclonal antibodies that do not bind the prescursor using the conventional end-peptide immunization techniques of Saido A and B combined with monoclonal antibody technology of Goding et al because of the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies and Takeda et al teach that antibodies with high sensitivity and specificity for amyloid peptide, including AB1-40 are desired. One would have been motivated to make screen for free-end specific monoclonal antibodies to eliminate the residual cross-reactivity of the monoclonal antibody BA-27(a) of Takeda and because Takeda et al teach that the prior art assays lack sensitivity and specificity and that highly specific monoclonal antibodies are useful for the detection of AB1-40 and AB1-42 species *in vitro* and that unique antibodies would reduce the background and increase the

sensitivity of the immunoassay for AB1-40. One of ordinary skill in the art would have a reasonable expectation of success given the demonstrated immunogenicity of the C-terminal epitope of AB1-40 as shown by Takeda and the success of Saido A for the N-terminal epitope and that Saido A teaches that similar approaches will be applicable to resolving the differential carboxy terminal processing of AB peptides.

Claims 23 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999),Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal ofBiological Chemistry, 268(33):25239-25243, 1993; herein after Saido B) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claim 14 above and further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994).

The teachings of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal fo Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) are set forth above. The references as combined fail to teach single chain antibodies.

Seubert et al teaches the use of antibodies that bind AB peptides in *in vitro* or *in vivo* assays that screen for inhibitors of AB peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "... the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, VL, VH, and other fragments." Seubert et al also teach that "It would

also be possible to employ recombinantly produced antibodies (immunoglobulins) and variation thereof as now well described in the patent and scientific literature. See, for example EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full pargraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of a single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the free-end, C-terminal specific monoclonal antibody according to the combination of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) in view of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001; hereinafter Saido A), Saido et al (The Journal fo Biological Chemistry, 268(33):25239-25243, 1993; herein after Saido B) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) above, by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produce that bind AB peptides are useful in a variety of detection techniques for use in screening or diagnostic assays.

Status of Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Acting Supervisor, Mark Navarro can be reached on 571-272-0861.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy
Primary Examiner
Art Unit 1645